ABSTRACT

Immunological testing of combined LELTE / saccharide dendrimers. (in Czech)

Alan Kádek

(Department of Biochemistry, Faculty of Science,
Charles University, Prague, Czech Republic)

CD69 is a widespread receptor of the immune system cells. Although a physiological ligand for this receptor is still unknown, in Laboratory of protein architecture its affinity towards a range of compounds including calcium, carbohydrates and charged compounds such as carboxylated calixarenes, has been proved. Moreover, a pentapeptide sequence LELTE derived from a mycobacterial chaperonine protein hsp65 has been recently identified as a ligand for CD69 representing a "danger" signal for the immune system. However, this peptide is not immunoactive *per se*, but only after its presentation within the multivalent environment of its parent protein, or after artificial dimerization using bi- or polyfunctional reagents.

In this thesis I evaluate for four newly synthesized compounds their *in vitro* immunological effects on cellular signalization, proliferation, natural killing of tumors and on induction of apoptotic cell death in immunocytes. The tested compounds present LELTE peptide through attachment to a cyclopeptidic RAFT scaffold $(K\text{-}K\text{-}K\text{-}P\text{-}G)_2$ through the ε-amino groups of lysine residues, alone or in combination with a carbohydrate α-GalNAc epitope. The ability of such scaffolds to activate human PBMC lymphocytes is enhanced in compounds, which possess both peptide and carbohydrate ligands. Moreover, all compounds are inactive from the point of view of activation-induced apoptosis of lymphocytes. However, triggering of CD69 by compounds containing only LELTE sequences inhibited natural killing *in vitro*. The activation abilities make the combined peptide / carbohydrate RAFT glycoconjugates suitable for evaluation in experimental animal tumor therapies *in vivo*.

Keywords: combined dendrimers, lymphocyte activation, tumor killing, apoptosis.